Research and Development Update

Secretary's Council for Public health Preparedness

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Biodefense for the 21st Century

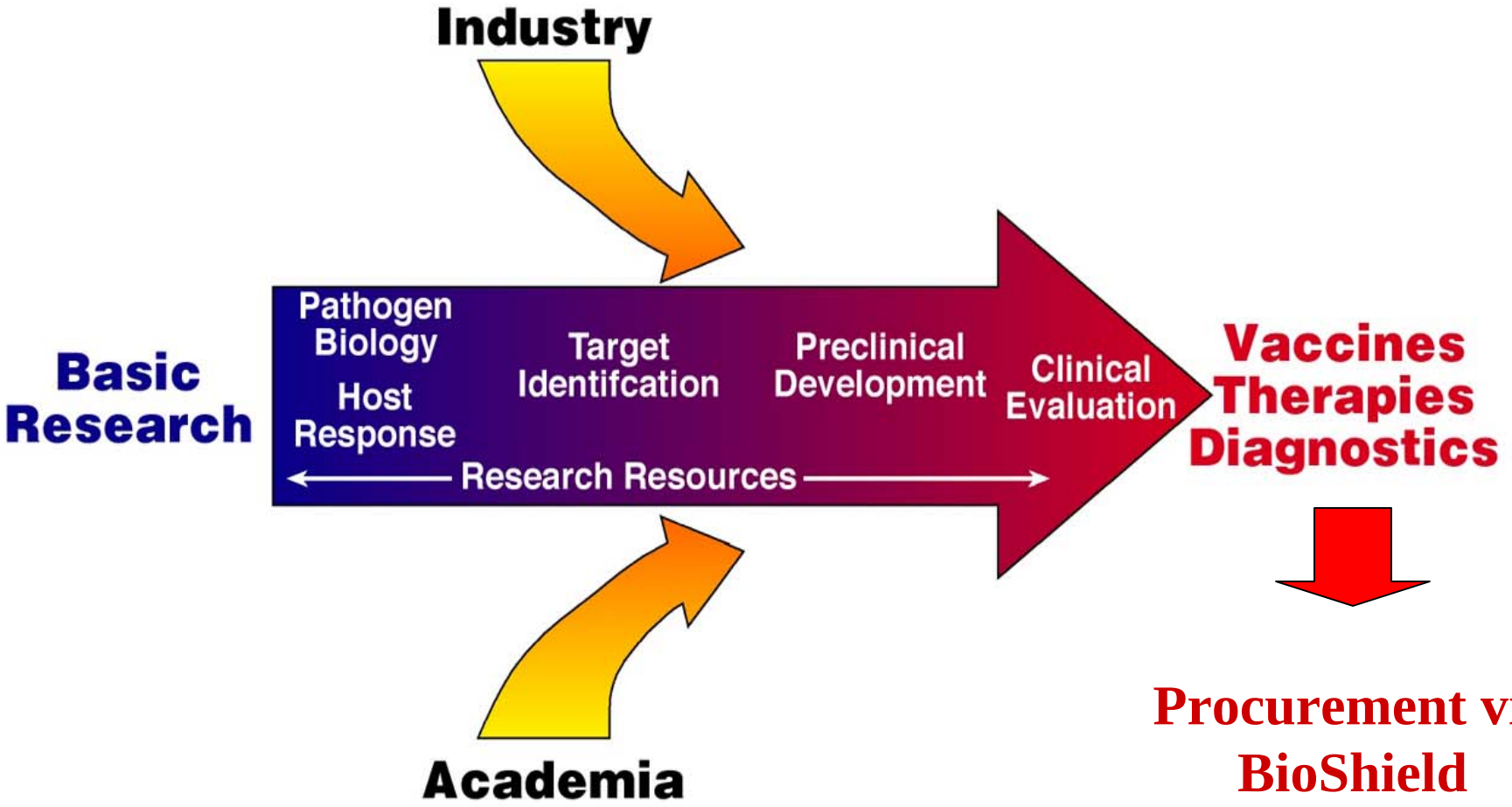
- **On 28 April 2004, HHS Secretary Tommy G. Thompson along with DHS Secretary Tom Ridge and DoD Deputy Secretary Paul Wolfowitz, announced the presidential directive "*Biodefense for the 21st Century*."**

- **This Presidential Directive follows a comprehensive evaluation of biological defense capabilities and provides a blueprint for our future biodefense program.**

Biodefense for the 21st Century

- **Essential Pillars of nation biodefense**
  - **Threat Awareness**
    - **Anticipation of Future Threats**
  - **Prevention and Detection**
  - **Surveillance and Detection**
  - **Response and Recovery**
    - **Capabilities required for response will be based on interagency-agreed scenarios that are derived from plausible threat assessments.**
    - **Mass Casualty Care**
    - **Risk Communication**
    - **Decontamination**
    - **MEDICAL COUNTERMEASURE DEVELOPMENT**
- **HHS will continue to lead the effort to ensure the development and availability of sufficient quantities of safe and efficacious medical countermeasures to mitigate illness and death in the event of a biological weapons attack.**

Medical Countermeasures Pipeline



Procurement via BioShield

Tools for defining requirements

- **Attack Scenarios**
  - Enables evaluation and comparison of various threats
- **Mathematical models of medical outcomes**
  - Detailed understanding of the impact of an attack
  - Provides an ability to evaluate various consequence management policies and countermeasures
- **Tabletop exercises**
  - Respond to attack scenarios
  - Evaluate government and local capabilities to respond
  - Assist in understanding of community and public response

Bioterrorism Attack Scenarios

- Department of Homeland Security has lead responsibility
  - Directorate of Science and Technology
- A means of understanding and comparing various threats
- Based largely on intelligence
  - National programs – old and new
  - Terrorist intentions and capability
- Heavily dependent on scientific and technical knowledge of agents and delivery mechanisms
  - Significant knowledge gaps become apparent
- Important in judgments on size of stockpile
- Research on the threat agents will improve the quality of the scenarios

Evaluating the Effectiveness of Countermeasures

- **Modeling medical consequences and effectiveness of response**
  - **HHS responsibility**
  - **Uses mathematical models to estimate casualties from an attack scenario and impact on the medical care system**
  - **Can be used to evaluate the effectiveness of various medical countermeasures**
    - **Pre event vaccination**
    - **Post exposure vaccination**
    - **Post exposure antibiotics**
    - **Quarantine and isolation**
  - **Value of the models is dependent on the validity of the assumptions**
  - **Highly sensitive to estimations of infectious dose, transmission rate(Ro), incubation period**
  - **HHS has begun a program to develop the best models for evaluation of medical countermeasures**
  - **Knowledge gaps become evident and inform research agenda**

Smallpox Models

- **Independent and different approaches**
  - **Halloran and Longini (Emory)**
  - **Burke and Epstein (Hopkins/ Brookings)**
  - **Glasser (CDC)**
  - **Eubank (Los Alamos)**
- **Agreement on basic assumptions derived from epidemiological experience**
- **Preliminary findings;**
  - **For small and medium attacks surveillance and containment (ring vaccination) will work well**
  - **Only very large attack may require rapid large scale vaccination**

Anthrax Models

- Independent and different models
  - Ron Brookmeyer (Johns Hopkins)
  - Nathaniel Hupert (Cornell)
  - Larry Wien (Stanford)
  - Michael Boechler (I E M)
- Agreement on underlying assumptions based on animal studies and very limited epidemiological data
- Preliminary findings
  - Differing approaches to modeling result in similar findings
  - Estimation of infectious dose and spore clearance mechanisms requires additional research
  - Time of initiating post-exposure antibiotics has large impact on numbers of fatalities

Setting Goals and Priorities

- **Research and Development - NIAID**
  - **Blue Ribbon Panels**
  - **Published on NIAID web site**
  - **DoD laboratories, DARPA – military focus**
- **Major Acquisitions – Interagency process**
  - **WMD Medical Countermeasures Subcommittee**
    - **OSTP, HSC, NSC oversight**
  - **Policy Coordinating Committee**
  - **Deputies Committee**
- **Strategic National Stockpile (SNS)**
  - **Intergovernmental Committee for the Composition of the Strategic National Stockpile**

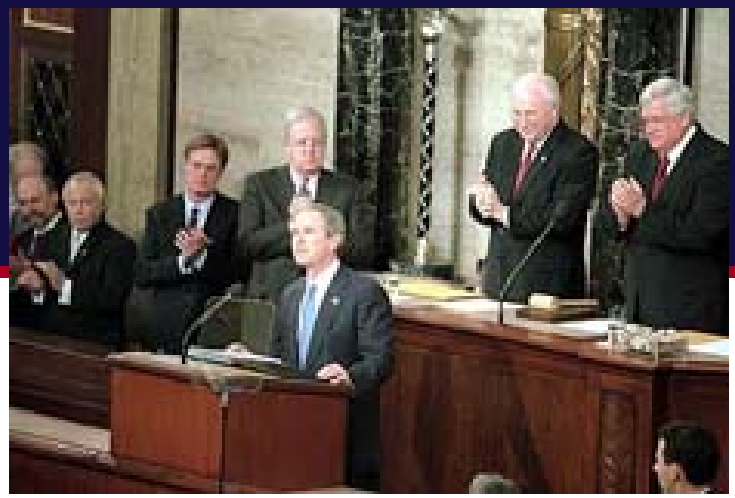
WMD Medical Countermeasures Committee

- Broad multiagency participation
- Prioritize federal initiatives
  - Address immediate and long-term needs
  - Recommend national requirements for vaccines, drugs, antitoxins, diagnostics
  - Represent needs of civilian and military
- Coordinate research, development, and acquisition efforts of key federal agencies: HHS, DHS, and DOD
- Develop acquisition and budget options for presentation to Policy Coordinating Committee (Assistant Secretary level) and the Deputies Committee
- Identify research and development gaps

WMD Medical Countermeasures
Authority

- **Presidential Directive (NSPD-17/HSPD-4, Dec 2002)**
  - **Counterproliferation Technology Coordination Committee (CTCC) to "improve interagency coordination of USG counterproliferation research and development efforts"**
- **White House charter (Spring 2003)**
  - **Medical Countermeasures Committee and Subgroups to carry out CTCC medical CBRN defense functions**

Project BioShield



BioShield was announced by President Bush in his State of the Union address on January 28, 2003.

The DHS appropriations bill (PL 108-90) signed by President Bush on 1 October 2003 provided **$890 million in discretionary funds in FY2004 and created a discretionary reserve of $5.6 billion to fund the program through FY2013.**

Funding is available for countermeasures once production of licensable products is judged scientifically feasible. **HHS will be the procuring authority**.

Potential BioShield Procurements Under Consideration

- rPA anthrax vaccine
- Anthrax treatment products (adjuncts to antibiotics)
- Next generation smallpox vaccine
- Botulinum antitoxin (Equine)
- Recombinant plague vaccine
- Botulinum vaccine
- Anti-radiation drugs and Chemical antidotes

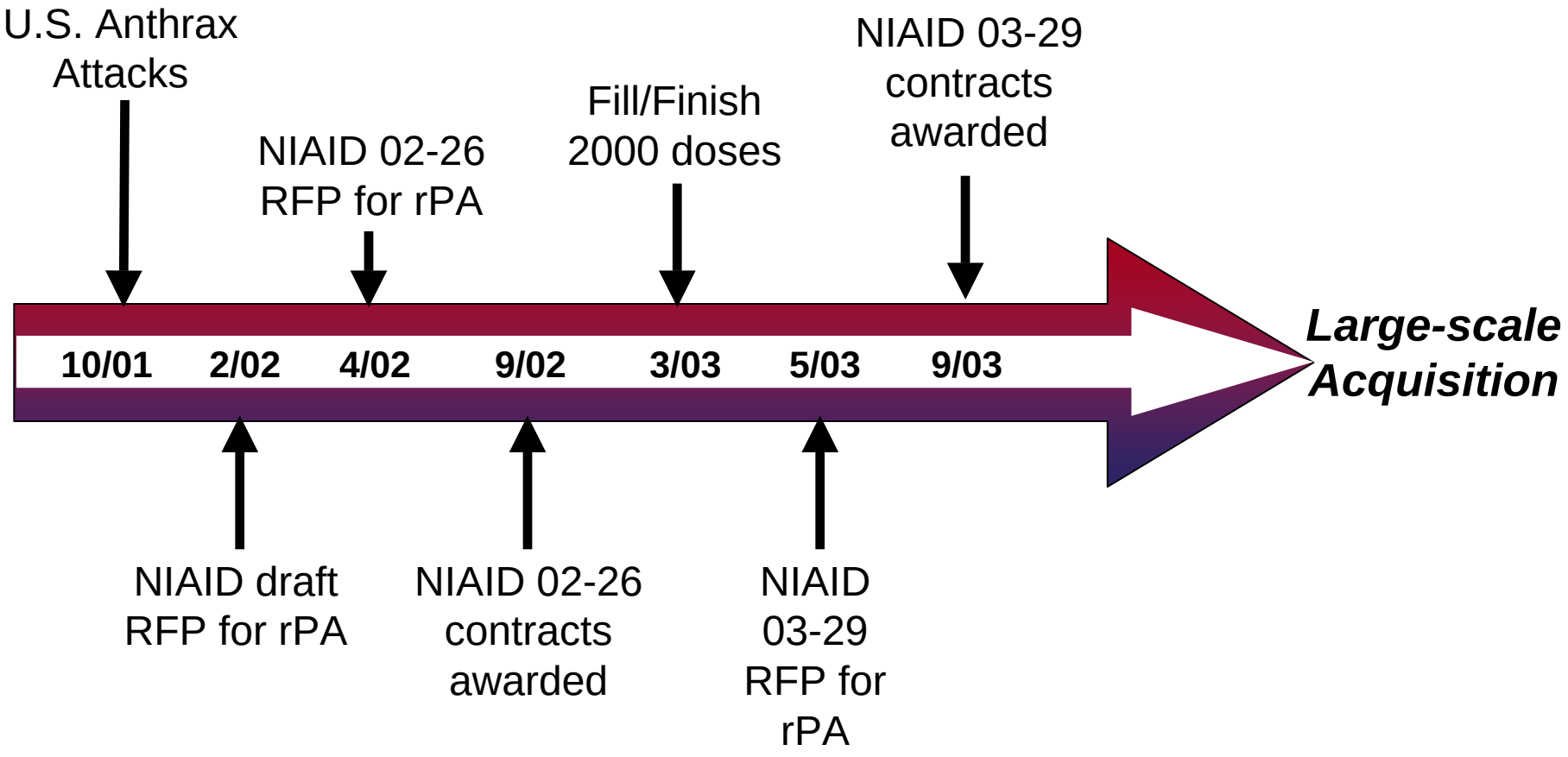
Potential Future Candidates for BioShield Procurement

- Ebola-Marburg vaccine
- Rift Valley Fever Vaccine
- Novel antibiotics/antinfectives
- Novel antiviral drugs
- Polyclonal human anthrax and botulinum antitoxins from transgenic animals
- 3rd Generation anthrax vaccine

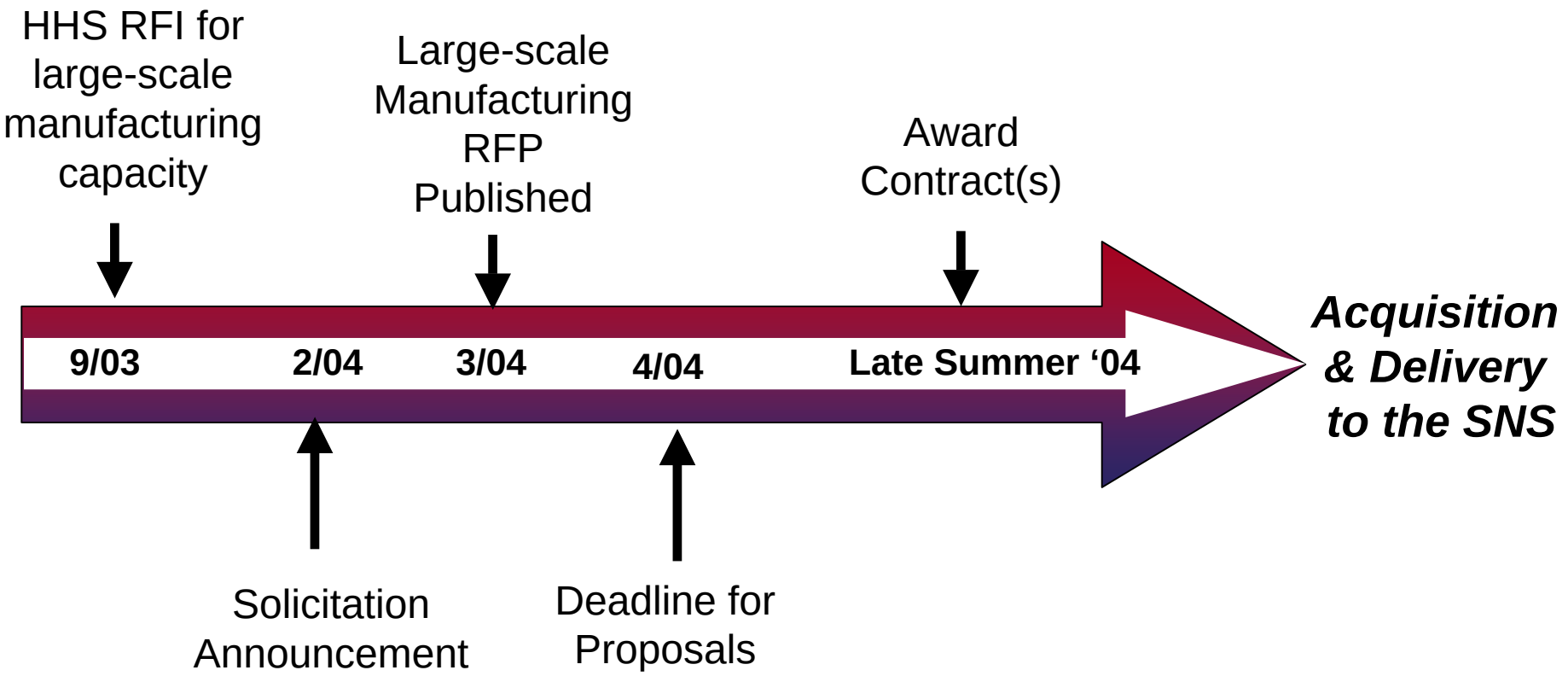
Features of the DHHS Next Generation (rPA) Anthrax Vaccine Program

- **Three-stage contracting strategy**
  - **Stage 1: Research and Early Development (NIAID)**
  - **Stage 2: Advanced Development (NIAID)**
  - **Stage 3: Large-scale Production & Acquisition (HHS)**
- **Aggressive timelines; milestone-driven**
- **Competitive contracts**
- **Goal: licensable product in the SNS**
- **Licensing strategy will utilize the FDA "Animal Rule"**

Timeline for Anthrax rPA Vaccine Development



Timeline for Large-scale Anthrax rPA Vaccine Acquisition



Anthrax Vaccine Questions

- Critical questions – interim answers
- What size stockpile is enough? 75 million doses?
  - What will be needed in the event of an attack or more than one attack?
  - What will be the public demand in the event of an attack ?
  - What is the value of vaccine after the attack?
    - Antibiotic sparing
    - Protection for residual contamination
  - What vaccination policy should be followed?
- How much pre-event vaccination is needed ?
  - First responders
  - Dense urban populations

Third Generation Anthrax Vaccine

- **Disadvantages of the 2nd generation rPA vaccine**
  - **Finite shelf life at 4^0 C**
    - **Cannot be stored frozen or lyophilized to extend useful product life**
  - **Administered by injection**
    - **Large scale vaccination campaign would greatly overburden the public health system**
- **What the government will need. An anthrax vaccine that :**
  - **Has a very long shelf life – possibly frozen or dried**
  - **Is easily administered by minimally trained personnel**
    - **Transcutaneous**
    - **Nasal**
    - **Oral**
  - **Generates antibody to PA and, possibly, LF and capsule**
  - **Can be produced a low cost**

Anthrax Treatment

- Antibiotic treatment alone may be insufficient after onset of disease even with state of the art intensive care
  - 45% (5/11) case fatality in 2001 anthrax attacks
- Toxin known to be present after vegetative bacteria are killed
- Antitoxin products as adjuncts to antibiotics offer significant promise
  - Anti-PA monoclonal antibodies
  - Anti-PA polyclonal antibodies
  - Protein inhibitors of protective antigen
  - Small molecule inhibitors of EF and LF
- Other antibacterial products might offer promise against antibiotic resistant anthrax
  - Lysins

Anthrax Treatment : Acquistion Challenges

- Promising candidate products are in differing stages of development
- Effectiveness of most is unproven
- Comparison between products is difficult
  - Effectiveness of polyclonal vs. monoclonal antibodies
  - Effectiveness of other inhibitors vs. antibodies
  - Differing modes of administration and pharmacokinetics
- Cost effectiveness is a significant consideration

Anthrax Treatments: HHS strategies

- **Initiate programs for comparative testing**
  - **Standardized, validated protocols**
  - **In vitro testing of antibody products – CDC**
  - **Small animal challenge models – NIAID**
- **Staged procurement over three years being considered**
  - **Will add most advanced treatment product(s) to stockpile**
  - **Allows development of newer candidates to proceed until value is proven**
  - **Provides time for additional comparative testing**
  - **May result in procurement of several products**

Antitoxin Treatments for Anthrax
Request for Information

- **Request for Information:**
  - **Release Date: March 30, 2004**
  - **Response Date: May 1, 2004**
  - **POC Marissa.Miller@hhs.gov**
- **Availability of commercial products or products in advanced development including but not limited to:**
  - **Monoclonal anti-PA antibodies, polyclonal anti-anthrax antibodies and human immunoglobulin**
  - **Mutant toxins, therapeutic proteins, enzymes, lysins, and protease inhibitors**

Future Solutions to Anthrax Threat

- **Widespread immunization of major population centers**
  - **Will require a new vaccine delivery technology and an affordable vaccine**
- **Stockpile of anthrax treatments that will work against multiple antibiotic resistant organisms**
  - **Novel antibiotic or antinfective product(s)**
  - **The most effective anti-toxin product(s)**
- **Timeline – Five years or less**

Safer Smallpox Vaccine

- Up to 65 million persons have contraindications to NYCBH vaccines
- Modified Vaccinia Ankara is lead candidate
- NIH funded R&D program for MVA development
- Two contracts awarded in February 2003
  - Bavarian Nordic
  - Acambis
  - Phase 1 trials have demonstrated immunogenicity
  - Non-human primate studies show protection from monkeypox
- NIH Advanced Development award(s) for MVA in mid-late 2004
- VaxGen independently developing LC16m8

Smallpox Vaccines: Unanswered Questions

- **How long can we rely on traditional NYCBH vaccines?**
  - **Known incidence of adverse events**
  - **Evidence for higher than expected incidence of myopericarditis**
  - **Increasing public resistance to vaccination**
- **Will demand for safer vaccines require a turnover of the stockpile to newer alternatives when they become available?**
- **How much are we willing to pay for a national stockpile of safer smallpox vaccines?**
- **Will the proven value of NYCBH vaccines to control smallpox be a critical factor in the decision ?**

Botulism Countermeasures

- Botulism is a significant threat to food and beverage supply
- A multivalent vaccine is in development by DoD and NIAID
  - Will have limited civilian use
- Principal civilian countermeasure is antitoxin
  - Multivalent product needed – 7 serotypes
  - Binds circulating toxin – prevents disease progression
  - Has no effect on bound toxin
  - Must be given early to be effective
  - Forward deployment may be the best strategy but greatly increases the amount required
- Best current option is despeciated Equine antitoxin

Botulinum Antitoxin (Equine)

- **Contract with Cangene for process development and processing of equine plasma from the military program**
  - **Will produce heptavalent product**
- **Two CDC contracts initiated for immunization of horses and collection of plasma**
  - **Sufficient plasma for 200,000 treatments**
- **Acquisition contract for processing plasma planned for late 2004**

Potential Future Acquisitions

- **Recombinant Plague Vaccine**
  - DoD and NIAID supported
  - F1 and V antigens
  - F1 and V fusion protein
- **Recombinant Botulism Vaccine**
  - Recombinant toxin fragment produced in Pichia pastoris
  - DoD - Bivalent AB vaccine
  - NIAID – research on CDEF antigens
- **Dominant requirement is for military use**
  - Civilian requirement small but important

Potential Future Acquisitions

- **Ebola – Marburg Vaccine**
  - **Promising research results**
- **Tularemia Vaccine**
- **Rift Valley Fever Vaccine**
  - **Stalled development**

- **Level of bioterrorist threat and potential utilization policy for vaccines undecided**
- **RVF and Ebola vaccines have important public health value in middle East and Africa**